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(6*R*,9*S*,13*R*,14*S*)-7,8-Didehydro-3,7-dimethoxy-17-methyl-6-phenylmorphinan-4,6-diol

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.006 Å
R factor = 0.044
wR factor = 0.106
Data-to-parameter ratio = 14.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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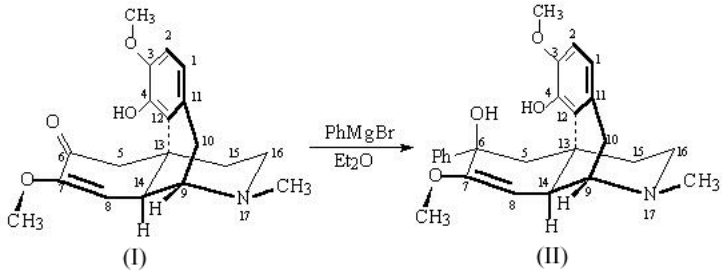
The title compound, $C_{25}H_{29}NO_4$, (II), was prepared by the reaction of (9*S*,13*R*,14*S*)-7,8-didehydro-3,7-dimethoxy-4-hydroxy-17-methylmorphinan-6-one, (I), with phenylmagnesium bromide. Compound (II) is a tetracyclic alkaloid with four chiral centers. The piperidine ring adopts a chair conformation, while the other two aliphatic rings are in twisted chair conformations. Compound (II) is the exclusive product, which means that, because of the steric effect, the phenyl anion stereoselectively attacks the opposite side away from the original phenyl group.

Comment

(9*S*,13*R*,14*S*)-7,8-Didehydro-3,7-dimethoxy-4-hydroxy-17-methylmorphinan-6-one, (I), is an important natural product which has been used to ease pain, to decrease blood pressure and to diminish inflammation. In order to study the stereochemistry of the reaction of (I) with phenylmagnesium bromide, the crystal structure of the title compound, (II), was determined by X-ray diffraction methods.

The results show that (II) is a tetracyclic alkaloid with four chiral centers. By comparing the structure of (II) with that of (I) (Iijima *et al.*, 1978; Hitotsuyanagi *et al.*, 1994), the newly formed chiral center of (II) was shown to be 6*R*. The N17/C9/C13–C16 piperidine ring adopts a chair conformation, while the C9–C14 and C5–C8/C14/C13 aliphatic rings adopt twisted chair conformations. Compound (II) is the exclusive product, which means that, because of the steric effect, the phenyl anion stereoselectively attacks the opposite side away from the original substituted phenyl group. The stereoselectivity of the phenyl anion is greater than that of the hydride anion on (I) (Li *et al.*, 2002).



(I) (II)

The C—C bonds within the benzene rings have normal aromatic values. The two methoxy groups are coplanar with the attached benzene ring and with the C7═C8 double bond and its substituents, respectively. The bonds O1—C3 and O4—C7 of 1.390 (5) and 1.374 (4) Å, respectively, are shorter than those of common C—O single bonds [O1—C19 and O4—C18 are 1.402 (8) and 1.410 (4) Å, respectively]. These facts indi-

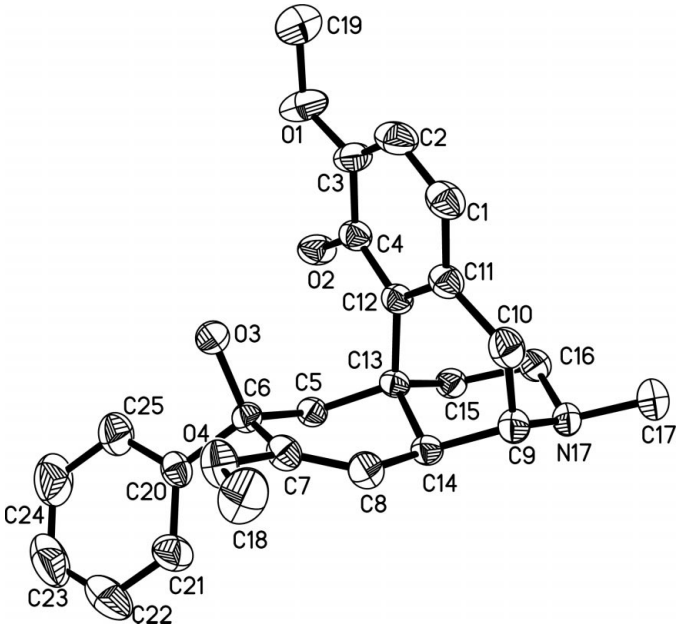


Figure 1
View of the molecular structure of compound (II), with ellipsoids at the 30% probability level.

cate that there exists p-π conjugation between O1 and the benzene ring, as well as O4 and the C7═C8 double bond.

The bond angle of 125.9 (4)° for O1—C3—C2 is larger than that of 113.6 (4)° for O1—C3—C4. It is assumed that this conformation will minimize the van der Waals interaction between the H atom on C2 and the C19 methyl group. The C18 methoxy group exhibits the same phenomenon. This kind of angle-opened arrangement of a methoxy group was also found in *r*-1,*c*-2,*t*-3,*t*-4-1,3-bis(4-methoxyphenyl)-2,4-bis[2-(5-methylbenzoxazolyl)]cyclobutane (Zhang *et al.*, 2001) and *r*-1,*c*-2,*t*-3,*t*-4-1,3-bis(4-methoxyphenyl)-2,4-bis[2-(5-phenyl-1,3,4-oxadiazolyl)]cyclobutane (Zheng *et al.*, 2001).

Experimental

Under an N_2 atmosphere, a solution of 0.66 g (2 mmol) of (I) in 20 ml of anhydrous THF was added to 8 ml of PhMgBr (8 mmol, 1.0 mol l^{-1}) in THF solution and stirred at room temperature for 12 h. The reaction mixture was poured into 50 ml of 1.0 mol l^{-1} NH_4Cl solution and extracted with $CHCl_3$. After drying over anhydrous Na_2SO_4, the solvent was evaporated, and the residue was purified by column chromatography on silica gel, eluting with 8:0.15:0.05 EtOAc/CH_3OH/Et_3N to give 0.56 g of (II). Yield: 70%, m.p.: 496–498 K, $[\alpha]_D^{25}$ = −41.3° ($CHCl_3$), IR (KBr): 3200 (*m*, *br*), 2929 (*s*), 1657 (*s*), 1606 (*m*), 1485 (*s*), 1279 (*s*), 1206 (*s*), 1153 (*m*), 1057 (*s*, *br*), 853 (*m*), 802 (*m*), 731 (*m*) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.37–7.24 (5H, *m*), 6.76 (1H, *d*, 8 Hz), 6.59 (1H, *d*, 8 Hz), 6.30 (1H, *br*), 4.71 (1H, *s*), 3.85 (3H, *s*), 3.80–3.60 (3H, *m*), 3.38 (3H, *s*), 3.20–2.95 (4H, *m*), 2.40 (1H, *s*, *br*), 2.70 (3H, *s*, *br*); 2.01–1.95 (3H, *m*) p.p.m.; ^{13}C NMR: 158.02, 147.22, 145.09, 144.44, 130.06, 127.90, 126.40, 125.03, 124.95, 118.69, 108.90, 97.62, 74.94, 57.97, 55.94, 54.52, 50.15, 47.93, 44.40, 42.20, 35.87, 35.61, 24.47 p.p.m.

Crystal data

$C_{25}H_{29}NO_4$
M_r = 407.49
Orthorhombic, $P2_12_12_1$
a = 11.710 (4) Å
b = 13.177 (4) Å
c = 14.236 (5) Å
V = 2196.6 (13) Å^3
Z = 4
D_x = 1.232 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 782 reflections
θ = 2.5–22.6°
μ = 0.08 mm^{-1}
T = 293 (2) K
Prism, colorless
0.28 × 0.24 × 0.20 mm

Data collection

Bruker SMART CCD area-detector diffractometer
φ and ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.976, T_{max} = 1.000
9147 measured reflections
3861 independent reflections
2017 reflections with $I > 2\sigma(I)$
R_{int} = 0.049
θ_{max} = 25.0°
$h = -13 \rightarrow 9$
$k = -15 \rightarrow 15$
$l = -15 \rightarrow 16$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.106
S = 0.96
3861 reflections
275 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0417P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.14 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

O1—C3	1.390 (5)	C7—C8	1.319 (5)
O1—C19	1.402 (8)	C8—C14	1.505 (5)
O2—C4	1.361 (4)	C9—N17	1.492 (4)
O3—C6	1.445 (4)	C10—C11	1.522 (5)
O4—C7	1.374 (4)	C12—C13	1.546 (4)
O4—C18	1.410 (4)	C16—N17	1.480 (4)
C6—C7	1.508 (5)	N17—C17	1.468 (4)
C3—O1—C19	115.8 (6)	O3—C6—C5	111.3 (3)
C3—O1—C19^{i}	116.7 (6)	C8—C7—O4	126.0 (3)
C7—O4—C18	118.2 (3)	O4—C7—C6	109.4 (3)
C2—C3—O1	125.9 (4)	N17—C9—C10	117.9 (3)
O1—C3—C4	113.6 (4)	N17—C9—C14	108.3 (3)
O2—C4—C12	119.8 (3)	C15—C13—C12	108.3 (3)
O2—C4—C3	120.3 (3)	C16—N17—C9	114.3 (3)
O3—C6—C7	108.5 (3)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O2	0.84	2.39	3.088 (4)	141
O2—H2···N17^{i}	0.86	1.85	2.692 (4)	164

Symmetry code: (i) $\frac{1}{2}+x, \frac{1}{2}-y, 2-z$.

The H atoms were positioned geometrically and refined as riding on their parent atoms. The absolute configuration can not be determined from the diffraction data in the absence of significant anomalous dispersion, and has been assumed from that of the starting material; Friedel pairs were merged.

Data collection: *SMART* (Bruker, 1997); cell refinement: *SMART*; data reduction: *SAINT* (Bruker, 1997) and *SHELXTL* (Bruker, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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